Editorials

Practical Therapeutics in Patients With Renal Impairment

THE RELATIONSHIP between the amount of a drug in the body and the drug's effects has been recognized for almost 150 years.[1] In the middle of the 19th century, Buchanan appreciated that the brain content of the new anesthetic, ether, depended on the strength of the inhaled mixture and the arterial concentration of the compound. He calculated the amount of the anesthetic retained during induction and related it to the depth of narcosis.

Nearly a century later, Torsten Teorell, a Swedish physiologist, described the first physiologically based model of drug behavior.[2,3] In his view, drug disposition was accounted for by a five-compartment model that included renal elimination as one factor influencing the amount of a drug retained in the body. His model predicts that drugs eliminated by the kidneys would accumulate in patients with impaired renal function.

This projection was confirmed by Kunin and Finland in 1959 with their report of antibiotic accumulation in patients with renal failure.[4] During the next decade, investigations of many frequently used drugs documented the dependence of drug elimination on renal excretion.[5,6] The data on drug elimination in patients with impaired renal function remained limited and scattered through many specialty publications.

In 1970, Bennett and colleagues compiled the first extensive list of frequently used drugs in patients with renal impairment and provided practical guidelines for dosing at various levels of renal function.[7] Although this work included specific dosing recommendations for 72 drugs based on 78 references, scarcely three years passed before a supplement containing 69 additional drugs or changes and 130 references was required.[8]

The rapid proliferation of complex and effective new drugs has added to the challenge of rational drug therapy in patients with abnormal renal function. Nearly a third of the antibiotics currently prescribed were not available five years ago.[9,10] Selective agonists and antagonists of cell receptors and specific enzyme inhibitors are readily available, as are biosynthetic peptide hormones. Pharmacokinetic data in patients with decreased renal function are now available for more than 300 commonly prescribed drugs from over 600 reference sources.[10]

Adverse reactions to drugs occur three times more frequently in patients with impaired renal function.[11] Alterations in drug absorption, distribution, protein binding, metabolism, and excretion of drugs and metabolites seen in patients with renal impairment play an important role in the therapeutic or toxic response to a drug. These adverse responses are most likely the result of drug doses inappropriate for patients' level of renal function.

Since that first list, "the Bennett tables" containing specific dose recommendations for patients with impaired renal function have appeared every three to five years as journal articles, supplements to journals, and, most recently, in book form. They can be seen in the overly laden white coat pockets of many house-staff physicians and on the bookshelves of most hospital libraries. In intensive care and dialysis units, well-worn copies are usually labeled, "Do Not Remove From . . ." to avoid their inevitable disappearance into a coat pocket or black bag.

Because the kidneys are the major regulators of the internal fluid environment, clinicians must possess a basic understanding of the biochemical and physiologic effects of drugs in patients with renal disease. Elsewhere in this issue of the journal, Swan and Bennett present a concise overview of drug disposition in patients with impaired renal function.[12] They provide a rational basis for practical therapeutics and specific guidelines for drug dosing at all levels of renal function. The table presented in their review (Table 2) provides practitioners an updated starting point for the careful use of frequently prescribed medications in a population at risk for adverse drug effects.

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REFERENCES

1. Buchanan A: Physiologic effects of the inhalation of ether. London Med Gaz 1847; 39:715-717

2. Teorell T: Kinetics of distribution of substances administered to the body—I. The extravascular modes of administration. Arch Int Pharmacodyn Ther 1937; 57:205-225

3. Teorell T: Kinetics of distribution of substances administered to the body—II. The intravascular modes of administration. Arch Int Pharmacodyn Ther 1937; 57:226-240

4. Kunin CM, Finland M: Persistence of antibiotics in blood of patients with renal failure. J Clin Invest 1959; 38:1509-1519

5. Orme BM, Cutler RE: The relationship between kanamycin pharmacokinetics, distribution and renal function. Clin Pharmacol Ther 1969; 10:543-550

6. Dettli L, Spring P, Habersang R: Drug dosage in patients with impaired renal function. Postgrad Med J 1967; 46:32-35

7. Bennett WM, Singer I, Coggins CH: A practical guide to drug usage in adult patients with impaired renal function. JAMA 1970; 214:1468-1475

8. Bennett WM, Singer I, Coggins CH: Guide to drug usage in adult patients with impaired renal function—A supplement. JAMA 1973; 223:991-997

9. Bennett WM, Aronoff GR, Golper TA, Morrison G, Singer I, Brater DC: Drug Prescribing in Renal Failure: Dosing Guidelines for Adults. Philadelphia, Pa, American College of Physicians, 1987

10. Bennett WM, Aronoff GR, Golper TA, Morrison G, Singer I, Brater DC: Drug Prescribing in Renal Failure: Dosing Guidelines for Adults, 2nd Ed. Philadelphia, Pa, American College of Physicians, 1991

11. Jick H: Adverse drug effects in relation to renal function. Am J Med 1977; 62:514-520

12. Swan SK, Bennett WM: Drug dosing guidelines in patients with renal failure. West J Med 1992 Jun; 156:633-638

Autoimmune Disease and the Nervous System*

THE NERVOUS SYSTEM, once considered to be sequestered from normal immune surveillance, can be the target of an autoimmune attack. Myasthenia gravis has been proved unequivocally to be an autoimmune disease mediated by antibodies to the acetylcholine receptor (AChR).[1] The case for autoimmunity in the pathogenesis of multiple sclerosis, involving an inflammatory response in the white matter of the central nervous system, and the Guillain-Barré syndrome, involving an inflammatory response in the myelin sheath of peripheral nerve, is strong.

Myasthenia gravis, a disease characterized by fatigable

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